Nonbenzodiazepine Sedative-Hypnotics for Sleep Disorders

Summary

- Non-pharmacological therapy is effective and is the standard of care for the initial treatment of insomnia.
- When pharmacologic management is required, medication choice is based upon the individual characteristics and needs of the patient, including the type of sleep difficulty (e.g., sleep-onset insomnia, sleep maintenance insomnia, frequent awakenings, early morning awakenings, circadian rhythm disruption), treatment goals, prior treatment responses, comorbid conditions, other medications, and cost.
- The American Academy of Sleep Medicine (AASM) guidelines for the pharmacologic treatment of chronic insomnia in adults suggest the use of ramelteon or zaleplon for sleep-onset insomnia, eszopiclone or zolpidem for sleep-onset and sleep maintenance insomnia, and doxepin or suvorexant for sleep maintenance insomnia.[62207]
- The use of non-prescription drugs, dietary supplements, or herbal products (e.g., melatonin, tryptophan, valerian) for the treatment of chronic insomnia in adults is not recommended by the AASM guidelines.[62207]
- Although classified as a non-prescription herbal product in the U.S., melatonin is available by prescription in Europe under the brand name Circadin as a short-term monotherapy treatment for primary insomnia characterized by poor quality of sleep in patients who are 55 years or older.[60055]
- Patients should be re-evaluated if insomnia does not improve within 7 to 10 days after starting pharmacological therapy regardless of the medication used.

Pharmacology

Antidepressants

Doxepin is a tricyclic antidepressant and is believed to exert sleep maintenance effects due to a strong binding affinity for histamine H1 receptors, which allows the use of the drug as a sedative at doses lower than those required for major depressive disorder. [39684]

Nonbenzodiazepine Benzodiazepine-Receptor Agonists

Zolpidem, eszopiclone, and zaleplon are thought to induce sleep by subunit modulation of the GABA-A receptor chloride channel macromolecular complex. The main site of modulatory drug action is located within the GABA-A receptor complex on the alpha-subunit, which is known as the benzodiazepine (BZ) or omega receptor. Eszopiclone has a longer half-life (6 hours) than the other drugs in the class which contributes to improving sleep maintenance.[30571][29887][57789]

Melatonin Receptor Agonists

Ramelteon and tasimelteon selectively target the melatonin receptors MT1 and MT2, which are located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN functions as the internal clock of the body and regulates the 24-hour sleep-wake cycle. The MT1 and MT2 receptors are believed to be involved in the promotion of sleep and the maintenance of the normal circadian rhythm (shift between day and night), respectively, when acted upon by endogenous melatonin.[31359][56665]

Orexin Receptor Antagonists

Suvorexant and lemborexant exert their therapeutic effects through antagonism of orexin receptors. Suvorexant and lemborexant block the binding of wake-promoting neuropeptides orexin A and orexin B to the OX1R and OX2R receptors, subsequently suppressing the wake drive.[57780][64870]

Dietary or herbal supplements

Melatonin is an endogenous hormone secreted by the pineal gland that interacts with melatonin receptors. Synthesis and secretion of endogenous melatonin are controlled by enzymes secreted by the hypothalamus which are activated by darkness and depressed by environmental light. The activity of melatonin at the MT1, MT2 and MT3 receptors is believed to contribute to its sleep-promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep

regulation. Commercial melatonin products are primarily synthesized because of the potential for contamination from animal-based infectious prions and viruses, which may cause serious illness.[60056]

Non-prescription (OTC) drugs

Diphenhydramine and doxylamine are first-generation sedating antihistamines (H1-blockers) that competitively antagonize the effects of histamine on the H1 receptor to produce their non-specific centrally-mediated sedative effects.[63270]

Comparative Efficacy

Citation	Design/Regimen	Results	Conclusion
Dundar Y, Dodd, S, Strobl J, et al. Hum Psychopharmacol. 2004;19:305-22.[63268]	Systemic review and meta-analysis of randomized controlled trials comparing zolpidem and zaleplon (6 trials).	**Sleep quality:** Zolpidem vs. zaleplon **Adverse events:** Zolpidem vs. zaleplon **Withdrawal symptoms:** Zolpidem vs. zaleplon	Zolpidem was more likely to improve sleep quality but also more likely to cause withdrawal symptoms compared to zaleplon (7.1% vs. 1.5%). No significant difference in adverse reactions between zaleplon and zolpidem.
Staner C, Joly F, Jacquot N, et al. Curr Med Res Opin. 2010;26:1423-31.[63269]	Randomized, double-blind, two-period crossover study comparing zolpidem PO 10 mg tablet and zolpidem SL 10 mg tablet in patients with primary insomnia.	**Latency to persistent sleep (LPS):** Zolpidem SL significantly shortened LPS by 10.3 min vs. zolpidem PO. **Sleep onset latency (SOL):** Zolpidem SL significantly shortened SOL compared to zolpidem PO. Subjective sleep improvement or next-morning residual effects did not differ between the two formulations.	Zolpidem SL is more effective in reducing sleep latency compared to zolpidem PO when given in equivalent doses.

Ferracioli-Oda E, Qawasmi A, Bloch MH. PLoS One. 2013;8:e63773.[60018]	Meta-analysis of randomized, placebo-controlled trials examining the effects of melatonin for the treatment of primary insomnia. A total of 19 trials, n = 1,683.	**Improved sleep onset latency:** Melatonin vs placebo (weighted mean difference = 7.06 minutes) **Improved sleep time:** Melatonin vs. placebo (weighted mean difference = 8.25 minutes) **Improved sleep quality:** Melatonin vs. placebo (standardized mean difference = 0.22) No significant side effects observed.	Melatonin significantly improved sleep latency, sleep time, and sleep quality compared to placebo. Trials with higher doses and duration of treatment were associated with greater therapeutic effect.
Culpepper L, Wingertzahn MA. Prim Care Companion CNS Disord. 2015;17:10.4088/PCC.15r01798. [63270]	Systematic review of efficacy and safety of OTC agents for the treatment of insomnia. A total of 17 publications.	**Melatonin:** Significant positive effects were reported for sleep quality, sleep onset, and morning alertness vs. placebo. Overall, adverse effects were similar to placebo. **Diphenhydramine and doxylamine:** Failed to demonstrate consistent, positive improvements in objective and self-reported sleep measures.	Melatonin demonstrated consistent positive improvements in sleep quality with limited adverse effects. Diphenhydramine and doxylamine lack safety and efficacy data for the treatment of insomnia.

Drug Interactions

CNS Depressants

Concomitant administration of sedative-hypnotics with other drugs having CNS depressant properties (e.g., psychotropics, anticonvulsants, antihistamines, narcotic analgesics, anesthetics, ethanol) is expected to produce additive CNS depressant effects and may lead to psychomotor impairment or respiratory depression. Patients should be advised not to take these medications with alcohol. Patients should not take other hypnotic agents or non-prescription/dietary supplement sleep aids concurrently. Patients should also be encouraged to confine their activities to those necessary to prepare for bed after taking their hypnotic agent. Some agents may also cause pharmacokinetic interactions; for example, doxepin increases concentrations of ramelteon and patients should be closely monitored if these medications are used concurrently.[31359][39684][30571][29887][57780][57789][56665][64870]

CYP Inducers and Inhibitors

Many drugs from this class are primary CYP substrates. Concomitant administration in patients receiving CYP inhibitors or inducers may alter drug exposure, with the potential for affecting efficacy or tolerability.[39684][30571][31359][57780][56665][29887][57789][40912][34522][64870]

Medication	Primary CYP Substrates	Metabolic Drug Interactions
Diphenhydramine	CYP2D6	Use cautiously with inducers or inhibitors of CYP2D6
Doxepin	CYP2C19, CYP2D6	Use cautiously with inducers or inhibitors of CYP2C19 or CYP2D6
Doxylamine	None	
Eszopiclone	CYP3A4	Max dose with strong CYP3A4 inhibitors is 2 mg/night Monitor for decreased efficacy when using strong CYP3A4 inducers
Lemborexant	CYP3A4	Avoid use with moderate or strong CYP3A4 inhibitors Max dose with weak CYP3A4 inhibitors is 5 mg/night Avoid use with moderate or strong CYP3A inducers
Melatonin	CYP1A2	Use with strong CYP1A2 inducers or inhibitors not recommended
Ramelteon	CYP1A2	Contraindicated with strong CYP1A2 inhibitors (e.g., fluvoxamine) Use cautiously with inducers or inhibitors of CYP1A2, CYP3A4, and CYP2C9
Suvorexant	CYP3A4	Use with strong CYP3A4 inhibitors not recommended Limit dose with moderate CYP3A4 inhibitors to 5 mg/night, if efficacious Monitor for decreased efficacy when using strong CYP3A4 inducers
Tasimelteon	CYP1A2, CYP3A4	Use with strong CYP1A2 inhibitors not recommended Use with strong CYP3A4 inducers not recommended
Zaleplon	CYP3A4	Use cautiously with strong CYP3A4 inducers or inhibitors Monitor for decreased efficacy when using strong CYP3A4 inducers
Zolpidem	CYP3A4	Use cautiously with strong CYP3A4 inducers or inhibitors Monitor for decreased efficacy when using strong CYP3A4 inducers

Smoking

- The exposure of tasimelteon, a primary CYP1A2 substrate, in smokers was lower than in non-smokers and therefore the efficacy of tasimelteon may be reduced in smokers. Tobacco smoking causes CYP1A2 induction.[56665]
- Melatonin is primarily metabolized by CYP1A2. Patients who are tobacco smokers have increased melatonin clearance due to the induction of CYP1A2 by tobacco. [60053][60055]

Section A

Therapeutic Use Table

Indications	Diphenhydramine Hydrochloride	Doxepin Hydrochloride	Doxylamine Succinate	Eszopiclone	Lemborexant	Melatonin	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem Tartrate
Renal Impairment Dosing Adjustment						Yes					Yes
Hepatic Impairment Dosing Adjustment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
circadian rhythm disruption						Yes †					
delayed sleep phase syndrome						Yes †					
irregular sleep-wake disorder						Yes †					
jet-lag						Yes †					
non-24-hour sleep-wake disorder						Yes †			Yes		
shift work sleep disorder						Yes †					
insomnia	Yes	Yes	Yes	Yes	Yes	Yes †	Yes	Yes		Yes	Yes

Yes – Labeled
Yes † – Off-label

Section B

Top 20 Adverse Reactions / Side Effects Table

Adverse Reaction / Side Effect	Diphenhydramine Hydrochloride	Doxepin Hydrochloride	Doxylamine Succinate	Eszopiclone	Lemborexant	Melatonin	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem Tartrate
drowsiness	22.1%	>10%	Reported	8 - 10%	6.9 - 9.6%	>10%	3%	4 - 7%	>10%	5 - 6%	<8%
headache	2.5%	Reported	Reported	13 - 21%	4.5 - 5.9%	1 - 10%	Reported	7%	17%	30 - 42%	<19%
dizziness	2.5%	>10%	Reported	1 - 7%		Reported	4%	3%		7 - 9%	1 - 23.5%
abnormal dreams		Reported		1 - 3%	0.9 - 2.2%	Reported		2%	<10%	Reported	0.1 - 1%
xerostomia	>4.9%	>10%	Reported	3 - 7%				2%		>1%	3%
abdominal pain	Reported	<1%	Reported			1 - 10%				6%	Reported
appetite stimulation	Reported	1 - 10%	Reported	0.1 - 1%						0.1 - 1%	<0.1%
constipation	Reported	>10%	Reported			Reported				>1%	0.1 - 2%
fatigue	Reported	1 - 10%	Reported		6.9 - 9.6%		3%				1 - 3%
nausea		1 - 10%		4 - 5%		Reported	3%			6 - 8%	1 - 7%
nightmares		<1%			0.9 - 2.2%	Reported			<10%	Reported	0.1 - 1%
palpitations		<0.1%	Reported			1 - 10%		Reported		0.1 - 1%	2%
dyspepsia		>10%		2 - 6%		Reported				>1%	>1%
hyperhidrosis	Reported	1 - 10%				Reported				0.1 - 1%	0.1 - 1%
infection		<1%		3 - 10%				<2%	<7%		0.1 - 1%
urinary retention	Reported	>10%	Reported							<0.1%	<0.1%
blurred vision	Reported	>10%	Reported								2%
contact dermatitis	1 - 10%	1 - 10%		0.1 - 1%						0.1 - 1%	
dysgeusia		<1%		<34%						>1%	0.1 - 1%
skin irritation		23%									

Section C

Safety Issues Table

Safety Issue	Diphenhydramine Hydrochloride	Doxepin Hydrochloride	Doxylamine Succinate	Eszopiclone	Lemborexant	Melatonin	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem Tartrate
REMS											
MedGuide		Yes		Yes	Yes			Yes		Yes	Yes
acute myocardial infarction		X									
breast-feeding	X					X					
children		BBW									
complex sleep-related behaviors				BBW						BBW	BBW
drug-induced complex sleep-related behaviors				X						X	X
MAOI therapy		X									
narcolepsy					X			X			
pregnancy						X					
suicidal ideation		BBW									
tricyclic antidepressant hypersensitivity		X									
urinary retention		X									

X – Contraindicated
X-BBW – Contraindicated and Black Box Warning
BBW – Black Box Warning, Not Contraindicated
Yes – REMS or MedGuide is available